Editorial

Warfarin Sodium or Aspirin Therapy to Prevent Stroke in Nonrheumatic Atrial Fibrillation

Answered and Unanswered Questions*

THE ROLE OF WARFARIN sodium anticoagulation in preventing strokes in patients with atrial fibrillation is reviewed by Wipf elsewhere in this issue.[1] Although anticoagulation is a highly effective therapy, and we may get the impression that everyone with atrial fibrillation should be anticoagulated, many (maybe even most) patients with nonrheumatic atrial fibrillation should probably not be treated with warfarin. Why? The answers will be addressed by the following questions.

• *Who gets atrial fibrillation?*

One of the most striking features of atrial fibrillation is that it is a disease of aging. The prevalence in patients younger than 50 years is less than 1%, whereas the prevalence in those older than 80 is 10%.[2] The average age of onset of atrial fibrillation is 70 to 74 years,[3] and the median age of people with atrial fibrillation is 75.[2]

• *What is the stroke risk in nonvalvular atrial fibrillation?*

The stroke risk on average in untreated patients with nonvalvular atrial fibrillation is about 5% per year for overt stroke. Perhaps another 1% to 2% per year have peripheral embolization, transient ischemic attacks, or "silent" strokes detectable only by imaging.[4]

• *Does warfarin therapy reduce the stroke risk when used for primary prevention?*

Definitely. Five randomized trials of primary stroke prevention provided concordant results showing an average 68% reduction in the risk of stroke with warfarin therapy compared with no warfarin therapy.[5]

• *Does taking aspirin reduce the stroke risk when used for primary prevention?*

Probably. The estimated pooled reduction of stroke risk with aspirin therapy compared with that in controls is 36% in primary prevention studies.[5] The available trials had conflicting results. The Copenhagen AFASAK trial used a regimen of 75 mg a day and showed an 18% reduction in the incidence of stroke (not significant),[6] whereas the SPAF I [Stroke Prevention in Atrial Fibrillation] trial used a regimen of 325 mg a day and found a significant 44% reduction in the incidence of ischemic stroke or systemic emboli.[7]

• *Which is better for primary prevention, aspirin or warfarin?*

From the available trials, the risk reduction with warfarin therapy (about 68%) has been greater than with the use of aspirin overall (about 36%).[5] In one of the primary prevention trials, the use of aspirin was substantially less effective than warfarin therapy.[8] The largest trial that directly compared the use of aspirin and warfarin, SPAF II, randomly assigned 1,100 patients and found no significant benefit of warfarin therapy (international normalized ratio [INR] 2.0 to 4.5; mean, 2.6) over aspirin, 325 mg a day, in patients either older or younger than 75. Although there were nonsignificant trends suggesting a lower primary event rate in the younger cohort treated with warfarin (0.7% versus 1.3% per year), there were no statistically significant differences between aspirin and warfarin therapy in any of the end points.

• *In secondary prevention, which is more effective, aspirin or warfarin?*

A previous stroke or transient ischemic attack (TIA) has been identified as an important independent risk factor for subsequent events in multivariate analyses.[5,9,10] The European Atrial Fibrillation Trial (EAFT) specifically evaluated therapy in these high-risk patients with atrial fibrillation and previous stroke or TIA,[11] comparing the use of aspirin, 300 mg per day, with warfarin and with placebo. The use of aspirin for secondary prevention in the EAFT trial reduced the risk of recurrent stroke by an insignificant 14% (aspirin: 10% per year; placebo: 12% per year),[11] whereas warfarin therapy was clearly superior to the use of aspirin, reducing the stroke risk by 66% (warfarin: 4% per year; placebo: 12% per year). Another randomized trial in secondary prevention comparing therapy with the platelet inhibitor indobufen with warfarin therapy will be reported soon.[12] On the basis of the EAFT trial, warfarin is definitely the therapy of choice for patients with previous TIA or stroke.

• *Are these results generalizable to "real" patients?*

One problem with the available trials is that a rather special group of patients was entered. Two of the trials reported the percentage of all screened patients with atrial fibrillation who were entered, which was only 6% of patients in the Canadian Atrial Fibrillation Anticoagulation (CAFA) trial[13] and 8% in the Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) trial.[14] In both trials, more than half of otherwise eligible patients with atrial fibrillation were excluded because they had relative or absolute contraindications to warfarin therapy, including bleeding disorders, coexisting medical disorders, alcoholism, and social and psychological reasons. The mean age of patients entered was 67 to 68 in four of the primary prevention trials[7,13-15] and 74 in a single trial.[6] Thus, the primary prevention trials entered a fairly rigorously screened and relatively young group of patients selected to have a low risk of bleeding on warfarin therapy. Even in these carefully selected patients receiving warfarin, 10% to 38% of patients were withdrawn from therapy during the trials.[6,7,11,13-15]

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• *What are the data in patients older than 75 with atrial fibrillation?*

More than half of the patients with atrial fibrillation are older than 75. The SPAF II trial separately randomly assigned 385 patients older than 75 to warfarin therapy (INR 2.0 to 4.5) versus an aspirin regimen of 325 mg per day. The primary event rate (ischemic stroke or systemic emboli) was 3.6% on warfarin therapy compared with 4.8% with the use of aspirin, which was not significantly different ($P = .40$). Because intracranial hemorrhage was much more common in the warfarin-treated group, the overall rate of stroke with residual effects was similar with both treatments (4.6% per year on warfarin versus 4.3% per year on aspirin). Thus, despite careful patient selection and monitoring of anticoagulation, the risks of bleeding, especially intracranial hemorrhage, were substantial in patients older than 75 and appeared to nullify any benefit of warfarin therapy relative to aspirin in this age group. Although it can be argued that the bleeding rate in this trial was high due to the relatively high INR (mean, 2.6), it is also likely that extending anticoagulation to less rigorously selected patients with less intensive monitoring would increase the bleeding risk. Lower-intensity therapy in this age group is currently being tested in the SPAF III trial.

• *What are the risks of anticoagulation?*

In the atrial fibrillation trials in which relatively younger, rigorously selected cohorts with a mean age of 67 to 68 were entered, the risk per year of major bleeding was 0.4%,[15] 1.3%,[14] 1.5%,[7] 1.7% (SPAF II <age 75),[16] and 2.5%.[13] The trials that entered older patients, however, had higher yearly rates of major bleeding on anticoagulation that were 2.8% in the EAFT (mean age, 72),[11] 3.2% in the AFASAK trial (mean age, 74),[6] and 4.2% in the SPAF II study (mean age, 80).[16] The relatively low complication rates in these closely monitored trials are probably not representative of those in more routine settings. It seems a certainty that if the entry criteria or monitoring had been less stringent, the bleeding risks would have been higher. Extrapolating low bleeding rates in younger patients to older patients is probably unwise, because the incidence of major bleeding increases with age, with one study estimating that the risk of major bleeding increased by 46% per decade above the age of 40.[17] Bleeding risk also increases with the intensity of anticoagulation as measured by the INR.[17] Perhaps the most feared complication is intracranial hemorrhage, an adverse event as dire as an embolic stroke. In SPAF II, intracranial hemorrhage occurred at a rate of 0.5% per year in the cohort younger than 75 but at 1.8% per year in the cohort older than 75.[16] Other studies have documented that the risk of intracranial hemorrhage goes up substantially with age.[18,19] In one study, the risk of intracranial hemorrhage was increased by 40% with each decade in patients receiving anticoagulants, such that the risk in an 80- to 90-year-old patient would be 5.4-fold greater than in a 30- to 40-year-old.[19]

• *Can patients with atrial fibrillation at a low risk of stroke be identified?*

There are several ways of identifying patients with atrial fibrillation at a low risk of stroke, defined as a risk of less than 1% per year. Such patients would reasonably be treated with only aspirin, or perhaps nothing. It is clear that patients younger than 60 years with lone atrial fibrillation have a low stroke risk of less than 0.5% per year.[5,20] Lone atrial fibrillation is variably defined, but a usable definition is atrial fibrillation in the absence of a history of stroke or TIA, diabetes mellitus, angina, heart failure, or myocardial infarction.[5] Above the age of 60, the risk of stroke in lone atrial fibrillation goes up, being 1.6% per year in 60- to 69-year-olds, 2.1% per year in 70- to 79-year-olds, and 3.0% per year in those 80 or older when untreated.[5] The SPAF I investigators identified 26% of the persons who had a stroke risk of only 1% per year on placebo; these low-risk subjects had no hypertension, no previous stroke or TIA, no recent heart failure, no global left ventricular dysfunction by echocardiogram, and a left atrium of 2.5 cm per m^2 or less. Similarly, in SPAF II, the stroke rate was only 0.5% per year in predefined low-risk patients treated with aspirin; low-risk patients were those younger than 75 without a history of hypertension, thromboembolism, or recent congestive heart failure. This low-risk group constituted 43% of the patients entered who were younger than 75.[16] The risks, expense, and inconvenience of lifelong warfarin therapy are not merited in low-risk patients.

• *Can patients with atrial fibrillation at a high risk of stroke be identified?*

Yes, high-risk groups can be identified who are probably more likely to benefit from taking warfarin. One group clearly is patients with a previous stroke or TIA as noted earlier. Other risk factors for stroke identified from multivariate analyses have been hypertension, diabetes mellitus, recent heart failure, left ventricular dysfunction by echocardiogram, and a left atrial size of more than 2.5 cm per m^2.[5,9,10]

• *What should we do until more data are in?*

Based on the foregoing, I would offer the following recommendations for antithrombotic therapy. Although these in many respects agree with those offered by Wipf,[1] I view the administration of aspirin as an acceptable therapy in more situations. First, patients with contraindications to taking warfarin should be treated with aspirin or possibly nothing if in a truly low-risk category. Contraindications to taking warfarin are common in patients with atrial fibrillation. In a recent Swedish study, it was estimated that only 26.5% of all patients with atrial fibrillation would be candidates for anticoagulation.[21] This figure is concordant with the high exclusion rates in the anticoagulant trials.[13,14] Second, groups identified as having a low stroke risk should also be given aspirin or nothing. Patients younger than 60 with lone atrial fibrillation are at a low risk, as are aspirin-treated patients younger than 75 without risk factors as defined earlier. Third, the

great majority of patients older than 75 should be treated with aspirin based on the results of SPAF II, because of the lack of proven superiority of warfarin and the clear increase in bleeding risk. Ongoing trials will provide further data about the relative risk and benefits of lower-intensity anticoagulation in this age group. Fourth, in patients of any age with previous TIA or stroke, the use of warfarin is preferred based on the results of EAFT. Fifth, among all other patients with atrial fibrillation (those younger than 75 without lone atrial fibrillation who have not had a stroke or TIA and who do not have contraindications to warfarin), either warfarin or aspirin therapy is reasonable, with the use of warfarin more effective but more difficult to administer and associated with a higher bleeding risk. Warfarin use should be particularly considered if any of the aforementioned risk factors are present.

Thus, despite the clear-cut efficacy of warfarin therapy in highly selected patients with atrial fibrillation in the published trials, in the real world of patients with atrial fibrillation, probably at least 50% of patients should be taking aspirin (or even nothing if truly low risk), either because they have an inherently low risk of stroke or because the bleeding risks of long-term warfarin therapy are unacceptable. Whether even lower intensities of warfarin therapy will prevent strokes with an acceptable bleeding risk remains to be seen.

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